



**Orbscan Pachymetry – Implications of a
Repeated Measures and Diurnal
Variation Analysis
(Reprint)**

By

Morris R. Lattimore

Aircrew Health and Performance Division

and

**Sendor Kaupp
Steven Schallhorn
Robert Lewis**

**Naval Medical Center
San Diego, California**

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made at 8:00 and 11:00 a.m. and at 4:00 p.m. on 3 separate days to assess repeatability. Grouped data from 18 volunteer subjects were compared to the data of the test subject as well.

Results: Pachymetry accuracy on a calibrated standard was determined to be $\pm 2\mu\text{m}$ (standard deviation, $n=12$). Repeated measures on the subject demonstrated a mean standard deviation of $9.08\mu\text{m}$ for 750 thickness data points across the central 7 mm of the cornea; peripheral measurement points exhibited progressively greater variability than at the apex (analysis of variance; $P<0.0001$). A plot of thickness by corneal location and time of day exhibited a diurnal pattern, with the peripheral cornea exhibiting progressively greater thickness changes than the central cornea (two-way analysis of variance; $P<0.00001$). The data significantly correlated across days when all times of day were considered ($r=0.999$). However, thickness values obtained at 8:00 a.m. were significantly different across days (t test; $P<0.0002$). The subject's data correlated very well ($r=0.9996$) with the grouped volunteer data.

Conclusions: These data show this system to be useful in corneal research and in clinical settings. The data confirm early morning pachymetry to be highly variable. Additionally, the data not only indicate a diurnal variation of corneal hydration over time, but also imply the presence of a diurnal-based hydration gradient across the peripheral cornea, both of which can have significance for PRK, since excimer tissue ablation effectiveness is influenced by tissue hydration. Ophthalmology 1999; 106:977-981

Orbscan Pachymetry

Implications of a Repeated Measures and Diurnal Variation Analysis

Morris R. Lattimore, Jr., OD, PhD,^{1,2} Sandor Kaupp, MS,² Steven Schallhorn, MD,² Robert Lewis, IV, OD²

Introduction: Corneal thickness changes reflect alterations in hydration and metabolism. Ultrasound pachymetry determinations may be adversely influenced by fluctuations in tissue hydration, whereas optical systems are apparently unaffected by these fluxes. A recently marketed, optical-based, topographic mapping system (Orbscan; Orbtex, Inc.) uses anterior and posterior corneal surface data to calculate corneal thickness.

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Corneal thickness change can serve as an index for alteration in corneal hydration and metabolism.^{1,2} However, the

most commonly used method of measuring corneal thickness (ultrasound pachymetry) is apparently subject to physical effects of hydration change itself as it relates to ultrasound speed through the cornea.^{3,4} Those same studies indicated that optical pachymetry systems are apparently unaffected in their ability to detect such changes in corneal thickness, either secondary to intraocular surgery or to extended wear of soft contact lenses. Furthermore, an optical system has been shown to possess the ability to detect small, hydration-based, transient, corneal thickness fluxes as a result of the application of topical anesthetic.⁵

Repeated measurement of corneal thickness is complicated by the natural phenomenon of diurnal variation. Typically, the diurnal pattern is of maximum thickness on awakening after lid closure overnight; within approximately 2 to 3 hours after eye opening, the thickness reportedly decreases to a "normal" level.^{6,7} Kiely, Carney, and Smith,⁸ using a Haag-Streit optical pachymeter, found that the human cornea thins progressively throughout the day after awakening. The magnitude of diurnal change was $10 \mu\text{m}$

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¹ Naval Health Research Center, San Diego, California.

² Naval Medical Center, San Diego, California.

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centrally and 20 μm at 40° into the periphery. They also documented a diurnal change in central corneal curvature accompanying this diurnal thickness change.

Recently, a topographic system that possesses the ability to map corneal thickness has become available (Orbscan; Orbtex, Inc., Salt Lake City, UT). The system is optically based in that it uses slit-lamp-type beams and a computerized mapping of the projected beam edge to construct altitude maps of the anterior and posterior surfaces of the cornea; corneal thickness is calculated from the altitude data. Multiple scans were performed on one patient at regular intervals throughout the course of a day, and at select times on other days, to evaluate instrument precision. This assessment also served to provide a thickness profile of the normal cornea and its diurnal variation pattern in this one subject. As a test of this subject's similarity to other people, his data were additionally compared to those of 18 volunteer subjects. An optical pachymetry tool of this type, if accurate enough, could be of practical use in any number of clinical and basic research settings, particularly in the area of refractive surgery.

Methods

Instrumentation

The Orbscan system is a computerized corneal mapping device that obtains elevation information from both the anterior and posterior corneal surfaces. It uses a calibrated video and slit-beam system to noninvasively measure three-space points on the front and rear corneal surfaces. The three-space points are used to construct mathematical representations of the true topographic surfaces (i.e., maps of z [elevation] vs. x and y [horizontal and vertical coordinates]). Therefore, corneal thickness, surface curvature, or topographic maps and any number of elevation maps for all aspects of the eye can be constructed from the initially measured elevation data. The hardware consists of an optics acquisition head, a Pentium processor computer system (Intel Corp., Santa Clara, CA), an optional custom workstation, and an optional color printer.

The optical acquisition head scans the eye using vertical light slits, similar to slit-lamp beams, which are projected onto the cornea from a 45° angle, one from the left side of the eye and another from the right side. Twenty slit projections are sequentially "frame-grabbed" by a computer-controlled video card from the eye in a left-to-right succession using the left slit beam, then 20 more slit projections are sequentially grabbed from right to left using the right slit beam, thereby providing a total of 40 interlaced, captured images for computer analysis. A tracking system monitors involuntary eye movements and mathematically accounts for them to accurately piece together the mathematical surface being analyzed. The slit-beam edge reflections are analyzed in all of the 40 images at the levels of the anterior and posterior corneal surfaces, the anterior and posterior lens surfaces, and the anterior iris surface. Elevation and thickness or depth maps are then constructed from these data. The corneal thickness or pachymetry data are a construct of the difference between the elevations of the anterior and posterior surfaces of the cornea.

Methodology

One of the authors (MRL) and one technician (GM), both trained by an Orbtex representative, captured all data. Five 40-image

captures from the subject's right eye were sequentially obtained at each examination time (0800, 0930, 1100, 1300, 1430, and 1600 hours) in 1 day and at 3 select times on other days (0800, 1100, and 1600 hours), for a total of 45 fully analyzed examinations. Corneal pachymetry maps were accessed for specific thickness data points at the apex and at the four cardinal points (12-, 3-, 6-, and 9-o'clock positions) 1.0 mm, 1.5 mm, 2.0 mm, 2.5 mm, 3.0 mm, and 3.5 mm concentrically from the apex (Fig 1). Although the system provides a color-coded thickness map, key concentric ring and cross-hair marking points were deliberately selected for specific data extraction that could be repeatedly accessed and compared via statistical subroutines on a spreadsheet. This provided 25 pachymetry measurements per fully analyzed examination, 125 pachymetry measurements per time of day, and a total of 750 pachymetry measurements over the course of the entire day (plus 375 pachymetry measurements taken on the other days). The data were then analyzed by corneal position, measurement location, and time of day, as well as for variability by those same factors.

The mean preoperative thickness data from 18 other subjects who were scheduled to be treated with photorefractive keratectomy (PRK) were compared over time of day with the test subject's data. To minimize diurnal effects of the comparison, the mean 18-subject measurement time of 1130 hours (examination times ranged from 0956–1523 hours), group data were compared to the 1100-hour data for the test subject.

Additionally, further measurements on the test subject were also made at select times on other days in an effort to examine day-to-day variability. Five measurements each were taken at 0800 hours on a separate day, at 1100 hours on another day, and at 1600 hours on yet a third day.

Results

A calibrated surface was repeatedly scanned to assess accuracy of the estimated anterior surface elevation model. Calibrated surface data were very accurate with the mean standard deviation (SD) of 12 repeated measures equal to 2 μm over the entire measured 7-mm diameter anterior surface map (range, 1.2 μm centrally to 3.2 μm peripherally). These measurements were taken four times from three different calibrated surfaces of spherical shape (37.5 D, 47.54 D, and 54.57 D).

Figure 2 illustrates the SD of the repeated corneal thickness measurements on the subject by corneal position and time of day. The variability of the pachymetry data increased with the distance away from the corneal apex into the periphery (analysis of variance; $P < 0.0001$). The mean SD for all data was 9.08 μm , ranging from 2.83 to 16.72 μm . Generally, on analysis, the thicker the estimated point on the cornea, the greater the estimated variation. There was also statistically significant change in variability related to time of day (analysis of variance; $P < 0.01$). A measurement location analysis revealed the horizontal, peripheral positions to have greater variability than the vertical, peripheral positions (peripheral, horizontal SD = 14.7 μm ; peripheral, vertical SD = 11.1 μm).

Figure 3 depicts the same day, repeated-measures pachymetry data by corneal position and time of day (five independent estimates averaged over four positions at each radius). This permits the localized comparison of the corneal diurnal variation patterns sequentially across the entire corneal profile from apex to 3.5 mm into the periphery. The diurnal variation in corneal thickness, a well-documented phenomenon, is clearly visible. In addition, the amount of change in thickness increases progressively the farther from the apex the thickness is measured. The maximum diurnal variation at the apex was approximately 8 μm ; at the 3.5-mm

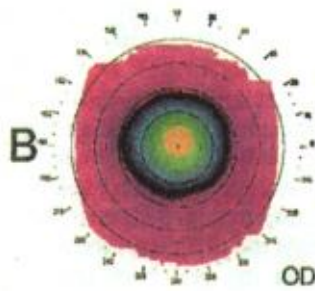


Figure 1. Sample Orbscan pachymetry map, illustrating the concentric ring and crosshair organization that allow measurements of corneal thickness at specific reference points.

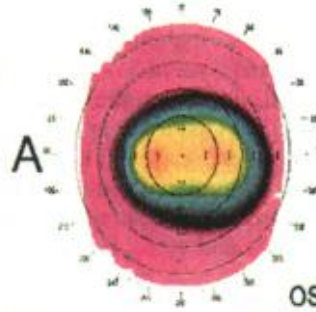


Figure 4. Sample of erroneous positioning. This map illustrates the appearance of two apparent minima on a cornea. This artifact presented only once in 45 repeated scans. Careful attention to proper positioning of the patient should eliminate this erroneous representation.

radius annulus, the maximum diurnal variation was 23 μm . These data are in agreement with the data reported by Kiely, Carney, and Smith,⁸ as mentioned previously.

The change in corneal thickness measured on any day was found to be significantly different for corneal position and time of day (two-way analysis of variance; $P < 0.00001$). When evening measurements are added (data captured at 1800 hours on yet another day, after the original data were analyzed), the diurnal pattern is somewhat sinusoidal in appearance, suggesting a cyclic pattern not previously indicated in humans but documented in the rabbit⁹ and the cat.²

The test subject used for this analysis possessed a somewhat thicker cornea than the typical or normal subject (based on personal clinical and research experience). To quantitatively compare corneal thickness profile characteristics, we sought to verify that this subject's profile was not significantly different from that of the

average subject. As stated in the Methods section, the mean preoperative thickness data from 18 other subjects who were scheduled to be treated with PRK were compared over time of day with the test subject's data. To minimize diurnal effects of the comparison, the mean 18-subject measurement time of 1130 hours (examination times ranged from 0956–1523 hours), group data were compared to the 1100-hour data for the test subject. The correlation was 0.9993, with a paired t test of $P = 0.73$ (i.e., the variability of the two data sets was not significantly different). Therefore, despite the fact that this subject has a uniformly thicker cornea, the data characteristics and corneal profile are representative of many other individuals.

Again, as stated in the Methods section, measurements on the test subject were also made at select times on other days in an effort to examine day-to-day variability. The data were matched for time: a two-tailed t test for paired data was used to probe for a statistical difference between the means, an f test for paired data was performed to assess variability between days, and a correlation was done to quantitatively examine the corneal profile characteristics. The 0800 data correlated at 0.9996, with an f test of $P = 0.60$, but with a t test of $P < 0.0002$; the 1100-hour data from 2 separate days had a correlation coefficient of 0.9994, an f test of $P = 0.57$, and a t test of $P = 0.22$; the 1600-hour data correlated at 0.9996, with an f test of $P = 0.47$ and a t test of $P = 0.32$. While the corneal thickness data were consistent (both in variability and repeatability) from at least 1100 hours onward on a day-to-day basis, the 0800 corneal thickness data were significantly different from day to day in this subject, although measurement variability at 0800 was not significantly different.

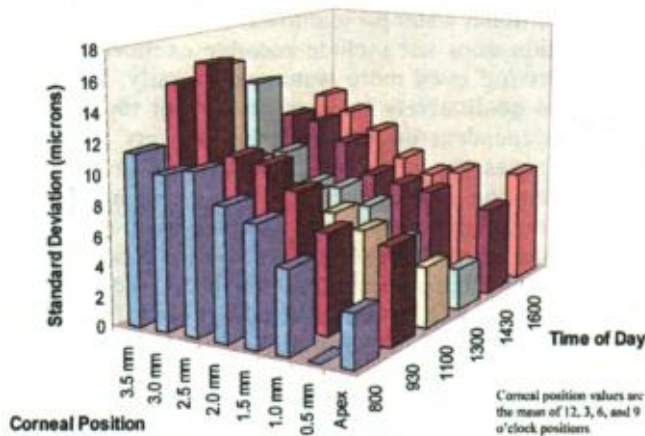


Figure 2. Orbscan pachymetry error distribution.

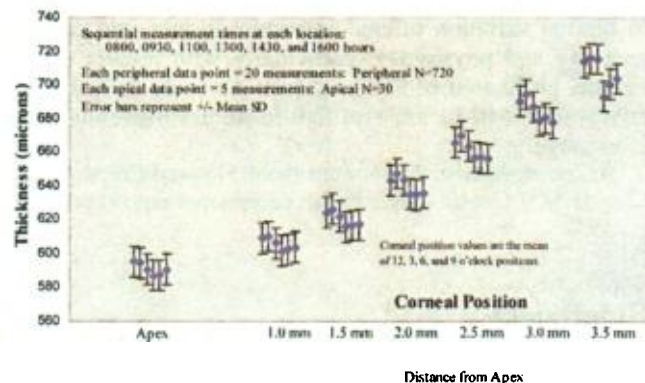


Figure 3. Corneal thickness diurnal variation profile.

Discussion

The accuracy of the surface maps of the calibrated standards yielded a mean SD of 2 μm (range, 1.2 μm centrally to 3.2 μm peripherally). Presuming similar accuracy for posterior maps, a simple mathematical addition of those errors would yield pachymetry SD values of greater than 2 μm but

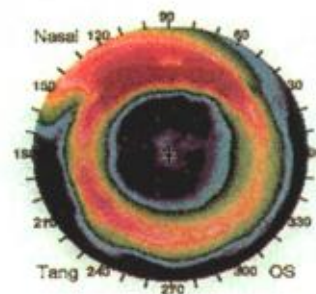


Figure 5. Constricted ablation zone, showing a 4-week postoperative PRK patient's apparently constricted ablation zone surrounded by a rim or convex ring of increased keratometric power.

perhaps less than 8 μm for a constructed pachymetry map. This is in general agreement with the experimental data obtained: the apical measurements had a mean SD of 5 μm (range, 3–7 μm), and the mean SD for the entire 7-mm-diameter area measured was 9.08 μm . Given the manufacturer's involuntary eye movement tracking system and the normal micromovement of any human subject's eye relative to the solidly fixed position of the calibrating spheres, there is good correlation between theoretic and actual error.

However, Figure 2 indicates the data were progressively more variable when going from the apex to 3.5 mm into the periphery (for both the calibrated standard and the subject). The source of instrument error that was the most obvious involved specular reflective glare of the small reflected light used to position each video image on top of the next. These reflective glare patterns interfered with the 3- and 9-o'clock data points at concentric positions 2.5, 3.0, and 3.5 mm from the apex. Either separate filtering systems (illumination and observation) or a chromatic system might serve to minimize these glare effects. An additional source of instrument error was associated with the edge-detection methodology; decreased room illumination was important in providing the image-analysis system with a good, clear, high-contrast beam edge. To minimize extraneous light, we covered both the subject's head and the instrument's data acquisition head with a towel.

There was one thickness map (of the 45 taken) that revealed apparent twin minima of the subject's cornea (Fig 4). This was proposed to be a result of operator error; positioning of the cornea too closely to the instrument would induce the fixed light sources to traverse the apical tissue at a skewed angle, traversing an artificially lengthened path centrally, obscuring the real apical minim, and revealing a false minim on either side of the apex (remember, the beam moves first from left to right, then from right to left). This artifactually thick central area would then be bordered bilaterally by two apparent minima simply as a function of induced transverse influence or error. This paired minimum was noted in the horizontal meridian, presumably because of the use of vertical slit beams. Horizontal beams, by this logic, would show two vertically displaced minima if the subject's cornea was too close to the instrument.

As stated in the Methods and Results sections, measurements on the test subject were also made at select times on other days in an effort to examine day-to-day variability. While the corneal thickness data were consistent (both in variability and repeatability) from at least 1100 hours onward on a day-to-day basis, the 0800 corneal thickness data were significantly different from day-to-day in this subject, although measurement variability was not significantly different. The presumed primary contributor to this early morning variation is time between awakening and measurement.^{6,7} In our subject, the time difference between awakening on different days was slightly more than 1 hour (70 minutes). This early waking hour hydration variability could have a significant effect on clinical procedures that rely on a presumed level of corneal hydration. Along this line, in terms of postoperative follow-up of patients with pseudophakia who are at risk of developing bullous kera-

topathy, it had previously been recommended that corneal thickness be measured only between 11:00 AM and 2:00 PM, unless hourly determinations are to be made.¹⁰ Of current importance is if patients being treated with PRK have been awake for less than 2 or 3 hours immediately before their treatment procedure, they may be subject to a certain degree of primary undercorrection because of a reduced ablation rate secondary to their more highly hydrated cornea.

The increased thickness toward the periphery, combined with greater diurnal variation in the periphery (Fig 3), denotes a shift in both hydration regulatory capacity and specificity of control, signifying the presence of a lateral hydration gradient extending from apex to periphery. The phenomena of RK and PK diurnal variation in both refraction and curvature^{11–14} could be related to this proposed lateral hydration gradient directly influencing central corneal shape over the course of a day.

Although postoperative PRK patients are apparently not subject to diurnal refractive and keratometric shifts,¹⁵ the demonstrated hydration variation across the corneal profile could serve as a source of error in PRK treatment. The greater hydration levels away from the corneal apex would progressively restrict the amount of tissue ablation per laser pulse. Therefore, the midcorneal ablation may be somewhat diminished, and the outer edges of a typical 6-mm ablation zone may be constricted. In essence, a 6-mm treatment ablation zone may actually be only an effective 4.5- or 5.0-mm refractive ablation zone because of the additional water present toward the periphery. This presentation does not include possible excimer "pulse" effects driving even more water peripherally. This end result can qualitatively be seen on corneal topographic maps, independent of manufacturer; patients' apparent ablation zones appear to be 4.5 to 5.0 mm in diameter rather than the treated 6 mm (Fig 5). An alternative explanation for the phenomenon seen in Figure 5 is that healing surface epithelium mounds over the ablation zone edge, creating the appearance of a decreased ablation diameter surrounded by a convex ring. Only further research will show which hypothesis regarding the underlying mechanism for this occurrence is correct.

In conclusion, the accuracy and variability (precision) of pachymetry measurements using Orbtex's Orbscan system proved to be acceptable for research use. Possible sources of error were identified for future system improvement. The relevance and implications of the thickness data pertaining to diurnal variation offered important insight into corneal anatomy and physiology, particularly with respect to the clinical evaluation of PRK patients. As such, the pachymetry system will be a useful tool in studies modeling PRK after surgery.

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